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# SYNTHESES AND EVALUATION AS GLYCOSIDASE INHIBITOR OF 1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL ANALOGS OF SALACINOL, A POTENT α-GLUCOSIDASE INHIBITOR ISOLATED FROM AYURVEDIC MEDICINE, *SALACIA RETICULATA*

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**Abstract** – *N*-Alkylated deoxynojirimycin (**10**) bearing the same alkyl chain as salacinol (**1**), a potent α-glucosidase inhibitor isolated from Ayurvedic traditional medicine, *Salacia reticulata*, was found to inhibit both rat intestinal maltase and sucrase as strong as **1**, while **10** has been reported to be inactive against glucoamylase G2 from *Aspergillus niger*. Its *O*-desulfate (**12**) was also found active against these enzymes, and characteristic sulfate anion moiety of **1** was found not essential for the α-glucosidase inhibitory activity.

## INTRODUCTION

In 1997 the authors isolated a potent α-glucosidase inhibitor salacinol (**1**) from Ayurvedic traditional medicine, *Salacia reticulata*[1,2] which has been used for the treatment of diabetes in Sri Lanka and India. The structure of **1** established by the X-ray crystallographic analysis was quite unique, the ring sulfonium ion being stabilized by the sulfate counter anion by forming a spirobicyclic-like configuration comprised of 1-deoxy-4-thio-D-arabinofranosyl cation and 1-deoxy-L-erythrosyl-3-sulfate anion. Several related sulfonium sulfates, kotalanol (**2**), ponkolanol (**3**) and salaprinol (**4**) have been subsequently isolated from the same *Salacia* species of plant.[3,4,5] The α-glucosidase inhibitory activities of **1-3** are potent, and have been revealed to be as strong as those of voglibose and acarbose, which are widely used clinically these

This paper is dedicated to the memory of the late Dr. John Daly, Scientist Emeritus of National Institutes of Health.

days.[1,2,3,4] Owing to both the high inhibitory activity and the intriguing structure, much attention has been focused on such sulfonium sulfate inner salts, intensive studies on the structure-activity relationships (SAR) based on their structure having been reported.[6,7,8,9,10,11,12,13,14,15,16] On the other hand, a large number of glycosidase inhibitors are based on azasugar derivatives with either five- or six-membered ring structures.[17,18] Among them, an azasugar (**5**) and deoxynojirimycin (**6**) were the representatives, and two derivatives of deoxynojirimycin namely miglitol (**7**) and *N*-butyldeoxynojirimycin (**8**) are currently in use as drugs for the treatment of Type II diabetes and Gaucher's disease, respectively.[17,18] On the basis of these background, the activity of *N*-alkylated analog of **5** with the same L-erythritol-type side chain (**9**) as salacinol had been tested independently by the authors[6,7] and by Ghavami and co-workers,[8,9,10] but **9** and related compounds were revealed inactive against α-glucosidases. By the intensive SAR studies by Szczepina and co-workers,[13] deoxynojirimycin *N*-alkylate (**10**) was also found inactive against glucoamylase G2 from *Aspergillus niger*.

In this paper, we present our own results on the inhibitory activity of **10** against rat intestinal α-glucosidases. As the *O*-sulfate anion moiety of **1** has been found not essential for the inhibitory activity by our recent findings on salacinol de-*O*-sulfate[11] (**11**), the activity of its de-*O*-sulfate (**12**) was also examined. Against the rat intestinal maltase and sucrase, both **10** and **12** showed almost nearly equal inhibitory activity to salacinol (**1**).

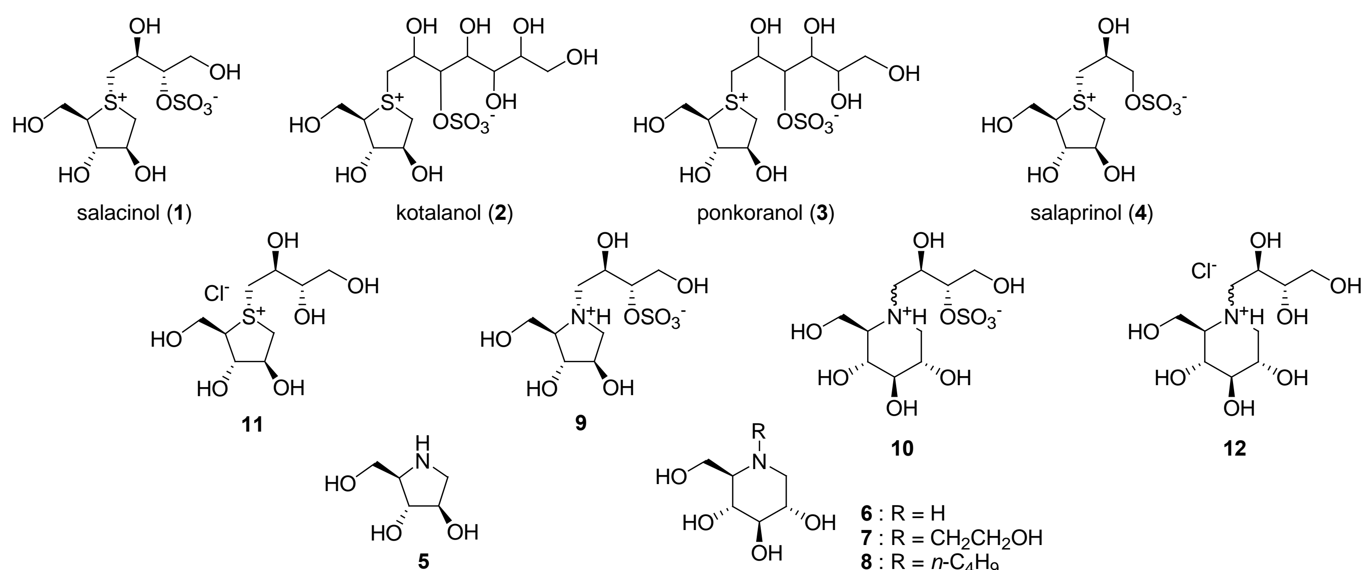


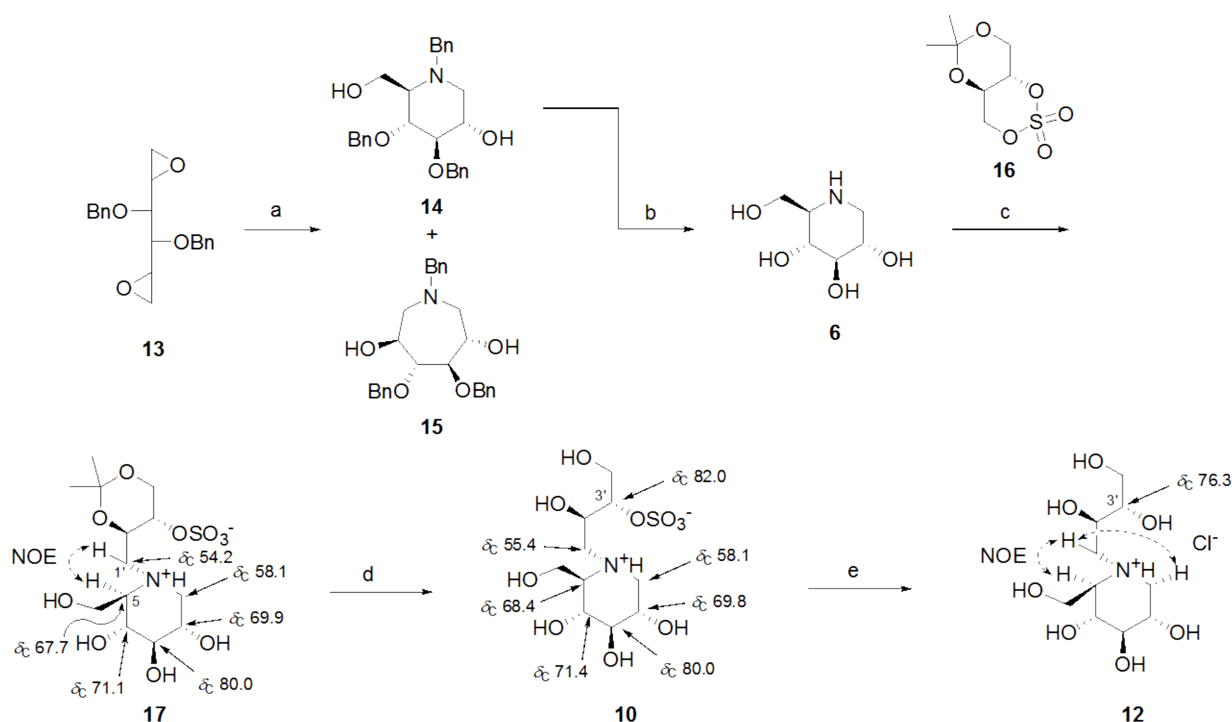

**Figure 1**

## RESULTS AND DISCUSSION

### Syntheses of Ammonium Analogs (10 and 12)

Deoxynojirimycin (**6**) was prepared starting from a bis-epoxide, 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-L-iditol (**13**) according to the literature.[19,20] Thus, treatment of **13** with benzyl amine gave *N*-benzyl-3,4-

di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol[19] (**14**) and *N*-benzyl-3,4-di-*O*-benzyl-1,6-dideoxy-1,6-imino-D-iditol[19] (**15**) in 43% and 36% yield, respectively. Hydrogenolysis of **14** on Pd-C in acetic acid gave deoxynojirimycine[19,21,22,23,24,25,26] (**6**) quantitatively. Without protection of the hydroxy groups, selective *N*-alkylation of **6** proceeded successfully by the treatment with a cyclic sulfate[11] **16** to give 1,5-dideoxy- 1,5-{*N*-[(2*S*,3*S*)-2,4-*O*-isopropylidene-3-(sulfooxy)butyl]iminoonium}-D-glucitol inner salt (**17**) in 75% yield. Compound **17** showed quasi-molecular ion peaks at *m/z* 388 and 386 due to $[M+H]^+$ and $[M–H]^-$, respectively, in its FAB mass spectrum. Its IR spectrum showed absorptions at 3359 $cm^{-1}$ (-OH), 2527 $cm^{-1}$ (-$N^+$H) and also at 1261 and 1223 $cm^{-1}$ (-$OSO_3^-$). The relative stereochemistry of the side chain was determined to be α-orientation in the present study on the basis of NOE studies, correlations between one of the methylene protons on C-1' and the methine proton on C-5 being detected. Acetal moiety of **17** was then removed using 0.5% hydrochloric acid at room temperature to give the desired ammonium sulfate, 1,5-dideoxy-1,5-{*N*-[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium}-D-glucitol inner salt (**10**). Finally, de-*O*-sulfation of **10** by action of methanolic hydrogen chloride gave 1,5-dideoxy-1,5-{*N*-[(2*S*,3*S*)-2,4-dihydroxybutyl]imino}-D-glucitol hydrogen chloride (**12**) in 84% yield. Reasonable upfield-shift of the signal due to 3'-methine carbon was observed in its $^{13}C$ NMR spectrum upon the hydrolysis. The α-orientation of the *N*-alkyl chain in **12** was also confirmed by the NOE correlations as depicted in Scheme 1.




**Scheme 1**. Reagents and conditions: (a) $BnNH_2$, $CHCl_3$, reflux; (b) $H_2$, 10% Pd-C, AcOH; (c) DMF, $Na_2CO_3$, 45 °C; (d) 0.5% aq. HCl, rt; (e) 5% methanolic HCl, rt.

### α-Glucosidase Inhibitory Activity

The glucosidase inhibitory activities of **10** and **12** were tested for rat intestinal α-glucosidases *in vitro*, and compared with those of salacinol (**1**) and its de-*O*-sulfate (**11**), as shown in Table 1. To these enzymes, the inhibitory activities of **10** were still potent, and $IC_{50}$ values against maltase and sucrase were 8.8 $\mu$M and 2.5 $\mu$M, respectively. It is noteworthy that **10** exhibit such selectivity toward enzymes, because **10** was reported to be inactive against glucoamylase G2 from *Aspergillus niger*.[13] Although de-*O*-sulfation of **10** resulted in slight decrease in inhibition against maltase, **12** still maintained the activity against sucrase to the same extent as **10**. Thus, present result revealed that *N*-alkylated ammonium salts with 6-membered ring structure (**10** and **12**) also function as sugar mimics against rat intestinal α-glucosidases. The sulfate anion moiety, which is characteristic of a series of salacinol and related analogs (**1**–**4**), seems to be not essential for the potent inhibitory activity on the basis of both our present and previous findings. Further investigations on the origin of both the strong α-glucosidase inhibitory activity and enzyme-selectivity of **1** and related compounds are in progress.

**Table 1.** $IC_{50}$ values (μM) of compounds **1**, **5**, **6**, **7**, and **9 – 12** against rat intestinal disaccharidases.

| Entry | Compound | Maltase | Sucrase |
|---|---|---|---|
| 1 | salacinol (**1**)[lit.2] | 9.6 | 2.5 |
| 2 | salacinol de-*O*-sulfate (**11**)[lit.11] | 14 | 3.5 |
| 3 | 5-membered azazugar (**5**)[lit.6] | 51 | 13 |
| 4 | aza analog (**9**)[lit.7] | 306 | 44 |
| 5 | deoxynojirimycin (**6**)[lit.6] | 0.8 | 0.2 |
| 6 | migritol (**7**)[lit.18] | 0.5 | 0.2 |
| 7 | compound (**10**) | 8.8 | 2.5 |
| 8 | compound (**12**) | 45 | 2.1 |

## EXPERIMENTAL

Mps were determined on a Yanagimoto MP-3S micromelting point apparatus, and mps and bps are uncorrected. IR spectra were measured on either a Shimadzu IR-435 grating spectrophotometer or a Shimadzu FTIR-8600PC spectrophotometer. NMR spectra were recorded on a JEOL JNM-ECA 500 (500 MHz $^{1}$H, 125 MHz $^{13}$C) or a JEOL JNM-ECA 700 (700 MHz $^{1}$H, 175 MHz $^{13}$C) spectrometer. Chemical shifts ($\delta$) and coupling constants ($J$) are given in ppm and Hz, respectively. Low-resolution and high-resolution mass spectra were recorded on a JEOL JMS-HX 100 spectrometer. Optical rotations were determined with a JASCODIP-370 digital polarimeter. Column chromatography was effected over Fuji Silysia Chemical silica gel BW-200. All the organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

### Aminocyclization of Bis-epoxide 13

According to the literature,[19] a mixture of bis-epoxide **13** (4.02 g, 12.3 mmol), $BnNH_2$ (6.8 mL, 62.3

mmol), and $CHCl_3$ (60 mL) was heated under reflux for 42 h. Work-up gave a pale yellow oil (11.2 g), which on column chromatography (*n*-hexane–AcOEt, 3:1) gave *N*-benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (**14**, 2.3 g, 43%) and *N*-benzyl-3,4-di-*O*-benzyl-1,6-dideoxy-1,6-imino-L-iditol (**15**, 1.9 g, 36%).

**14**: colorless needles (from *n*-hexane–AcOEt). Mp 107.5–109 °C (lit.,[19] 109 °C). $[\alpha]_D^{24}$ +6.0 (*c* 1.06, $CHCl_3$) [lit.,[19] +4 (*c* 1.1, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$: 1.82 (1H, br s, OH), 2.17 (dd, *J* = 11.5, 9.8, H-1ax), 2.35 (1H, br, s, OH), 2.47 (ddd *J* = 8.6, 3.2, 1.5, H-5), 3.06 (dd, *J* = 11.5, 4.5, H-1eq), 3.39/4.07 (each d, *J* = 13.5 Hz, $PhCH_2N$), 3.40 (dd, *J* = 8.6, 8.6, H-3), 3.64 (ddd, *J* = 9.8, 8.6, 4.5, H-2), 3.71 (dd, *J* = 8.6, 8.6, H-4), 3.88 (dd, *J* = 12.0, 1.5, H-6a), 4.02 (dd, *J* = 12.0, 3.2, H-6b), 4.72/4.90 (each 1H, d, *J* = 11.1 Hz, $PhCH_2O$), 4.73/4.92 (each 1H, d, *J* = 11.8 Hz, $PhCH_2O$), 7.25–7.38 (15H, m, arom.). Assignments for the H-1ax and H-1ex, and those for one of the methylene protons in the *N*-benzyl moiety and H-6a in the literature[19] were interchanged, and revised in the present study on the basis of 500 MHz $^1$H-NMR measurements.

**15**: colorless needles (from *n*-hexane–AcOEt). Mp 74.5–75.4 °C (lit.,[19] 77 °C). $[\alpha]_D^{24}$ +14.8 (*c* 1.13, $CHCl_3$) [lit.,[19] +15 (*c* 1.6, $CHCl_3$)]. $^1$H and $^{13}$C NMR spectroscopic properties of **15** were in good accordance with those reported.[19]

**Deoxynojirimycin (6)**

A suspension of 10% palladium-on-carbon (1.0g) in AcOH (6 mL) was pre-equilibrated with hydrogen. To the suspension was added **14** (1.74 g, 4.0 mmol), and the mixture was hydrogenated at rt for 19 h. The catalyst was filtered off, and the filtrate was evaporated. The remaining AcOH was then co-evaporated with benzene to give a pale yellow oil (1.01 g). The aqueous solution (15 mL) of the oil was treated with ion exchange resin IR120B. After filtration of the resulting mixture, the resin was washed with MeOH, and rinsed out with 5% aqueous ammonia. The rinsing was evaporated to give the title compound[19,21,22,23,24,25,26] **6** (641 mg, 98%) as a colorless solid, mp 194–195 °C (lit.,[19] 194–196 °C; lit.,[21] 199–199.5 °C; lit.,[23] 199–201 °C). $[\alpha]_D^{22}$ +41.6 (*c* 1.29, $H_2O$) [lit.,[19] +46 (*c* 0.9, $H_2O$); lit.,[21] +40.3 (*c* 1.47, $H_2O$); lit.,[23] +42.0 (*c* 0.1, $H_2O$)]. $^1$H NMR (500 MHz, $D_2O$) $\delta$: 2.43 (1H, dd, *J* = 12.3, 10.6 Hz, H-1ax), 2.51 (ddd, *J* = 9.6, 6.3, 3.2 Hz, H-5), 3.08 (dd, *J* = 12.3, 5.2 Hz, H-1eq), 3.20 (dd, *J* = 9.6, 9.2 Hz, H-4), 3.28 (dd, *J* = 9.2, 9.2 Hz, H-3), 3.46 (ddd, *J* = 10.6, 9.2, 5.2 Hz, H-5), 3.59 (dd, *J* = 11.8, 6.3 Hz, H-6a), 3.79 (dd, *J* = 11.8, 3.2 Hz, H-6b). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$: 51.3 (C-1), 63.1 (C-5), 63.9 (C-6), 73.5 (C-2), 74.1 (C-4), 81.0 (C-3).

**Coupling Reaction between the Cyclic Sulfates (16) and Deoxynojirimycin (6)**

A mixture of deoxynojirimycin (**6**, 500 mg, 3.06 mmol), cyclic sulfate[11] (**16**, 824 mg, 3.67 mmol), $Na_2CO_3$ (705 mg, 6.65 mmol), and DMF (1 mL) was stirred at 45 °C for 24 h. After dilution of the reaction mixture with MeOH, the resulting mixture was filtered, and the filtrate was concentrated at reduced pressure to give a pale yellow oil (1.16 g), which on column chromatography ($CHCl_3$–MeOH–$H_2O$, 9:5:1) gave 1,5-dideoxy-1,5-{*N*-[(2*S*,3*S*)-2,4-*O*-isopropylidene-3-(sulfooxy)butyl]-iminoonium}-D-glucitol inner salt (**17**, 890 mg, 75%) as a colorless oil, $[\alpha]_D^{24}$ +52.5 (*c* 0.5, MeOH). IR (neat): 3359, 2527, 1651, 1384, 1261, 1223, 1070, 1015 cm$^{-1}$. $^1$H NMR (700 MHz, $CD_3OD$) *δ*: 1.33/1.49 [each 3H, s, $(CH_3)_2C$]), 2.46 (1H, br d-like, *J* = *ca*. 9.5 Hz, H-5), 2.49 (1H, br dd-like, *J* = *ca*. 10.9, 10.9 Hz, H-1ax), 2.90 (1H, dd, *J* = 15.0, 8.0 Hz, H-1'a), 3.18 (1H, dd, *J* = 9.2, 9.2 Hz, H-3), 3.20 (1H, dd, *J* = 10.9, 4.9 Hz, H-1eq), 3.38 (1H, br d, *J* = 15.0 Hz, H-1'b), 3.43 (1H, dd, *J* = 9.5, 9.2 Hz, H-4), 3.55 (1H, ddd, *J* = 10.9, 9.2, 4.9 Hz, H-2), 3.85 (1H, dd, *J* = 11.6, 7.2 Hz, H-4'a), 3.89 (1H, dd, *J* = 12.0, 2.4 Hz, H-6a), 4.02 (1H, dd, *J* = 12.0, 3.0 Hz, H-6b), 4.05 (1H, ddd, *J* = 8.8, 7.2, 5.3, H-3'), 4.09 (1H, br dd, *J* = 8.8, 8.0 Hz, H-2'), 4.10 (1H, dd, *J* = 11.6, 5.3 Hz, H-4'b). $^{13}$C NMR (125 MHz, $CD_3OD$) *δ*: 20.3/28.0 [$(CH_3)_2C$], 54.2 (C-1'), 58.06 (C-6), 58.12 (C-1), 63.8 (C-4'), 67.7 (C-5), 69.9 (C-2), 70.5 (C-2'), 71.1 (C-4), 72.2 (C-3'), 80.0 (C-3), 100.5 [$(CH_3)_2C$]. FABMS *m/z*: (pos.) 388 $[M+H]^+$. FAB-HR-MS *m/z*: 388.1277 ($C_{13}H_{26}O_{10}NS$ requires 388.1278).

**1,5-Dideoxy-1,5-{*N*-[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]iminoonium}-D-glucitol Inner Salt (10)**

A solution of **17** (600 mg, 1.55 mmol) and 0.5% hydrochloric acid (8 mL) was stirred at rt for 2.5 h. After removal of the solvent at reduced pressure, the residue (540 mg) was purified on column chromatography (MeCN–$H_2O$, 3:1) to give the title compound **10** (414 mg, 77%) as a colorless oil, $[\alpha]_D^{23}$ +9.2 (*c* 1.55, MeOH). IR (neat): 3344, 2511, 1651, 1268, 1219, 1069 cm$^{-1}$. $^1$H NMR (700 MHz, $CD_3OD$) *δ*: 2.44 (1H, br dd-like, *J* = *ca*. 9.7, 9.7 Hz, H-1ax), 2.51 (1H, br, H-5), 2.76 (1H, br dd-like, *J* = *ca*. 14.0, 9.0 Hz, H-1'a), 3.21 (1H, dd, *J* = 9.2, 9.2 Hz, H-3), 3.22 (1H, br-d like, *J* = *ca*. 9.7 Hz, H-1eq), 3.26 (1H, m, H-1'b), 3.38 (1H, dd, *J* = 9.2, 9.2 Hz, H-4), 3.58 (1H, ddd, *J* = 9.7, 9.2, 4.8 Hz, H-2), 3.81 (1H, dd, *J* = 12.0, 4.4 Hz, H-4'a), 3.86 (1H, dd, *J* = 12.0, 3.6 Hz, H-6a), 3.92 (1H, dd, *J* = 12.0, 4.0 Hz, H-4'b), 3.99 (1H, dd, *J* = 12.0, 2.4 Hz, H-6b), 4.13 (1H, br ddd, *J* = *ca*. 9.0 4.0, 4.0 Hz, H-2'), 4.28 (1H, ddd-like, *J* = 4.4, 4.0, 4.0 Hz, H-3'). $^{13}$C NMR (175 MHz, $CD_3OD$) *δ*: 55.4 (C-1'), 58.1 (C-1), 59.1 (C-6), 62.1 (C-4'), 68.4 (C-5), 69.5 (C-2'), 69.8 (C-2), 71.4 (C-4), 80.0 (C-3), 82.0 (C-3'). FABMS *m/z*: (pos.) 348 $[M+H]^+$, (neg.) 346 $[M-H]^-$. FAB-HR-MS *m/z*: 348.0964 ($C_{10}H_{22}O_{10}NS$ requires 348.0965).

**1,5-Dideoxy-1,5-{*N*-[(2*S*,3*S*)-2,3,4-trihydroxybutyl]imino}-D-glucitol Hydrogen Chloride (12)**

A mixture of **10** (150 mg, 0.43 mmol) and 5% methanolic hydrogen chloride (7 mL) was stirred at rt for 1.5 h. After removal of the solvent at reduced pressure, the residue (128 mg) was purified on column chromatography ($CHCl_3$–MeOH–$H_2O$, 12:8:1) to give the title compound **12** (110 mg, 84%) as a colorless oil, $[\alpha]_D^{24}$ +2.8 (*c* 0.75, MeOH). IR (neat): 3283, 2492, 1651, 1080, 1034 $cm^{-1}$. $^1H$ NMR (500MHz, $CD_3OD$) $\delta$: 2.246 (1H, dd, *J* = 11.2, 10.4, H-1ax), 2.250 (1H, ddd, *J* = 9.2, 3.7, 2.6, H-5), 2.54 (1H, dd, *J* = 13.7, 6.3 Hz, H-1'a), 3.15 (1H, dd, *J* = 11.2, 4.9 Hz, H-1eq), 3.158 (1H, dd, *J* = 9.2, 9.2 Hz, H-3), 3.162 (1H, dd, *J* = 13.7, 6.1 Hz, H-1'b), 3.31 (1H, dd, *J* = 9.2, 9.2 Hz, H-4), 3.48 (1H, ddd, *J* = 10.4, 9.2, 4.9 Hz, H-2), 3.57 (1H, ddd, *J* = 6.0, 5.4, 3.8 Hz, H-3'), 3.62 (1H, dd, *J* = 11.2, 5.4 Hz, H-4'a), 3.72 (1H, dd, *J* = 11.2, 3.8 Hz, H-4'b), 3.77 (1H, ddd-like, *J* = 6.3, 6.1, 6.0, H-2'), 3.84 (1H, dd, *J* = 12.3, 3.7 Hz, H-6a), 3.98 (1H, dd, *J* = 12.3, 2.6 Hz, H-6b). $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta$: 55.7 (C-1'), 58.9 (C-1), 59.5 (C-6), 64.7 (C-4'), 68.6 (C-5), 70.28/70.33 (C-2, C-2'), 71.8 (C-4), 76.3 (C-3'), 80.5 (C-3). FABMS *m/z*: (pos.) 268 $[M]^+$. FAB-HR-MS *m/z*: 268.1381 ($C_{10}H_{22}O_7N$ requires 268.1396).

**Enzyme inhibition Assays**

Rat small intestinal brush border membrane vesicles were prepared and its suspension in 0.1 M maleate buffer (pH 6.0) was used as small intestinal α-glucosidase of maltase and sucrase. Test compound was dissolved in dimethylsulfoxide DMSO, and the resulting solution was diluted with 0.1 M maleate buffer to prepare the test compound solution (concentration of DMSO: 10%). The substrate solution in the maleate buffer (maltose: 74 mM, sucrose: 74 mM, 100 μL), test compound solution (50 μL), and the enzyme solution (50 μL) were mixed and incubated at 37 °C for 30 min. After incubation, the solution was mixed with water (0.8 mL) and was immediately heated by boiling water for 2 min to stop the reaction. Glucose concentration was then determined by the glucose-oxidase method. Final concentration of DMSO in test solution was 2.5% and no influence of DMSO was detected on the inhibitory activity.

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